

Notice of Allowability

Application No.

09/724,889

Examiner

Nashaat T. Nashed, Ph. D.

Applicant(s)

JULIEN ET AL.

Art Unit

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.


1. ☒ This communication is responsive to the amendment filed June 14, 2004.
2. ☒ The allowed claim(s) is/are 15, 16 and 29-31.
3. ☒ The drawings filed on 11 March 2004 are accepted by the Examiner.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) ☐ All b) ☐ Some* c) ☐ None of the:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).
 - * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
 6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
 - (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
 - 1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
 - (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.
- Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08),
Paper No./Mail Date 11/28/00 & 12/15/03
4. ☐ Examiner's Comment Regarding Requirement for Deposit
of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413),
Paper No./Mail Date _____.
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.


Nashaat T. Nashed, Ph. D.
Primary Examiner
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A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 14, 2004 has been entered.

The application has been amended as requested in the communication filed April 21, 2004. Accordingly, claims 17, 25, and 32-34 have been canceled, and claim 15, 16, and 29-31 have been amended.

Claims 15, 16, and 29-31 are under consideration.

The terminal disclaimer filed on June 30, 2004 disclaiming the terminal portion of any patent granted on this application, which would extend beyond the expiration date of U. S. Patent 6,303,342 has been reviewed and is accepted. The terminal disclaimer has been recorded.

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Randolph Ted Apple on July 8, 2004.

The application has been amended as follows:

(1) Amend claim 15 and 29 as shown bellow:

Claim 15: A method for preparing an epothilone D derivative having a methyl group at C-12 and a double bond between C-12 and C-13, which method comprises providing substrates including extender units to a non-Sorangium ~~S.~~ cellulosum host cell that expresses a modified functional Sorangium cellulosum cellulosem epothilone polyketide synthase (PKS), wherein said PKS comprises (a) Sorangium cellulosum EpoA, EpoB, EpoC, EpoD, and EpoF proteins and (b) a modified functional EpoE protein wherein said modification comprises at least one of: replacement of at least one acyltransferase (AT) domain with an AT domain of different specificity in module 7 and/or module 8; inactivation of a ketoreductase (KR) domain in module 7; inactivation of a methyltransferase (MT) domain in module 8; and addition of at least one of KR, dehydrogenase (DH) and enoylreductase (ER) activity

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in at least one β -carbonyl modification domain in module 7 and/or module 8, and recovering said epothilone D derivative from said host cell.

Claim 29: A method for preparing an epothilone D derivative having a methyl group at C-12 and a double bond between C-12 and C-13, which method comprises providing substrates including extender units to a non-*Sorangium S. cellulosum* host cell that expresses a modified functional epothilone polyketide synthase (PKS), said PKS comprising (a) *Sorangium cellulosum* EpoA, EpoB, EpoC, EpoD, and EpoF proteins and (b) a modified functional EpoE protein that lacks at least one activity encoded by a *Sorangium cellulosum* epoE gene and/or comprises at least one domain derived from a heterologous polyketide synthase, and recovering said epothilone D derivative from said host cell.

Claims 15, 16, 29-31 are allowed.

The following is an examiner's statement of reasons for allowance: The application discloses the nucleic acid encoding the gene cluster of epothilone from *Sorangium cellulosum*, and methods of modifying the polyketide synthases encoded by the gene clusters as well as methods of making epothilones A-D and their derivatives by recombinant methods. Originally, applicants elected to prosecute claims directed to a modified polyketide synthase epoE, which is the protein product of the *epoE* gene from the gene cluster. The original claims were rejected under U. S. C. 103 for reasons of record and the rejection made final. In response to the final rejection, applicants filed the RCE application accompanied by an amendment of the pending claims to be directed to a method of making epothilone D derivative using the modified *epoE* gene. Although epothilone D was a known compound to be produced in minor amounts relative to epothilone A and B in the prior art, its biosynthetic pathway and its relationship to epothilone B was not known. Applicants have shown that epothilone D is the immediate precursor to epothilone B and the gene product of *epoK* is responsible for the epoxidation of epothilone D to form epothilone B. Claims directed to method of making epothilone D were found allowable in the parent application, serial number 09/443,501, now U. S. P. 6,303,342. The filing of a proper terminal disclaimer over U. S. patent 6,303,342 obviated a possible obviousness double patent rejection. Similar claims directed to a method of making epothilone D derivative in which *epoD* is modified are allowed in copending serial number 09/724,876. Since the claimed method is not anticipated or obvious over the prior art of record, the claims are allowed.

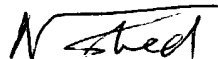
Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Nashaat T. Nashed, Ph. D.
Primary Examiner
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